D2 Cont retained within the capsule and the capsule is introduced into the tumor or next to the tumor.

16. (Twice amended) The pharmaceutical kit according to Claim 15, wherein the capsules and the prodrug are formulated so that the capsules, which are administered into a target or next to the target, and the prodrug can be administered by different routes of administration.

D3

22. (Amended) The capsule according to Claim 1 wherein the cytochrome P450 is encoded by a mammalian expression vector.

D4

REMARKS

Priority

The Examiner acknowledges receipt of the certified copy of the priority application filed in Denmark and states that "a translation of the DK 0352/96 application as required by 35 U.S.C. 119(b) has not been filed" (Office Action, page 2).

Applicants respectfully disagree. The certified copy of DK 0352/96 is in the English language. Therefore, the requirements of 35 U.S.C. §119(b) have been met.

Rejection of Claims 11-19 under 35 U.S.C. §112, first paragraph

Claims 11-19 are rejected under 35 U.S.C. §112, first paragraph "because the specification . . . does not reasonably provide enablement for a method of treating a tumor comprising administering to a subject in need thereof a therapeutically effective amount of the capsule of claim 1 and, either simultaneously or with a time span, a prodrug which is activated by cytochrome P450" (Office Action, pages 2-3). The Examiner states that "claims 11-19 remain rejected because the scope of claim 11 is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of methods of administering said capsule broadly encompassed by the claims" (Office Action, page 3). The Examiner further states that:

> [t]he guidance in the specification as seen in example 10, only provides guidance for the direct insertion of the capsules encapsulating cytochrome p450 producing cells into tumors (Office Action, pages 3-4)

and that:

> [t]here is no guidance for other results of administration. In particular there is no evidence that by systemic administration sufficient capsules would reach the target tumor to have any affect on the tumor (Office Action, pages 3-4).

In conclusion, the Examiner states that:

> applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including means of administration of a capsule encapsulating cytochrome P450 expressing cell (Office Action, page 4).

Claim 11 was previously amended to delete the phrase "according to claim 1" in the Amendment mailed to the U.S. Patent Office on July 18, 2000. Claim 11 has been further amended and is now directed to a method of treating a tumor comprising administering to a subject in need thereof a therapeutically effective amount of a capsule and, either simultaneously or with a time span, a prodrug which is activated by cytochrome P450, wherein the capsule comprises a porous membrane formed by a polyelectrolyte complex which encapsulates cells which express a cytochrome P450 gene, the membrane is permeable to the prodrug molecules, the cytochrome P450 gene and the cytochrome P450 expressed by the gene are retained within the capsule and the capsule is introduced into the tumor or next to the tumor.

Applicants have proved an enabling disclosure for the full scope of the claimed invention.

Rejection of Claim 5 under 35 U.S.C. §112, first paragraph

Claim 5 is rejected under 35 U.S.C. §112, first paragraph "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention" (Office Action, page 4). The Examiner states that the language "said capsule is formed from counter-charged polyeletrolytes" in Claim 5 is not supported by the original specification.

Claim 5 has been canceled, thereby obviating the rejection.

Rejection of Claims 1, 9, 21 and 22 under 35 U.S.C. §112, second paragraph

Claims 1, 9, 21 and 22 are rejected under 35 U.S.C. §112, second paragraph "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention" (Office Action, page 5).

The Examiner states that "[n]ewly amended claim 1 is rejected because the limitation 'wherein the prodrug molecules are converted into active drug molecules by cytochrome P450', is confusing because this limitation does not describe the capsule encapsulating a cytochrome P450 expressing cell, but rather appears to describe a method" (Office Action, page 5).

As amended, Claim 1 relates to a capsule comprising a porous membrane formed by a polyelectrolyte complex which encapsulates cells which express a cytochrome P450 gene, wherein the membrane is permeable to prodrug molecules, and the cytochrome P450 gene and the cytochrome P450 expressed by the gene are retained within the capsule.

The Examiner states that in Claim 9, "[i]t could be viewed that there is no antecedent basis in claim 1 for 'cytochrome P450 2B1' or is the intention of the applicant to further limit the cytochrome P450 of claim 1 to cytochrome P450 2B1" (Office Action, pages 5-6).

As amended, Claim 9 is directed to the capsule according to Claim 1 wherein the cytochrome P450 is cytochrome 2B1.

The Examiner states that Claims 22 is rejected because literal interpretation of this claim "means that the cytochrome P450 **protein** itself is in a mammalian expression vector" (Office Action, page 6). The Examiner further states that "[i]t is not normal for one of ordinary skill in the art to place a protein in an expression vector, unless applicants intent is to refer to the instant capsule as a 'expression vector'" (Office Action, page 6).

Claim 22 has been amended to recite the capsule according to Claim 1 wherein the cytochrome P450 is encoded by a mammalian expression vector.

Rejection of Claims 1-20 and 22 under 35 U.S.C. §102(a)

Claims 1-20 and 22 are rejected under 35 U.S.C. §102(a) "as being anticipated by Saller et al. (WO 97/01357)" (Office Action, page 6). The Examiner acknowledges that the "Saller et al. reference does not specifically teach the expression of cytochrome P450 within the encapsulated cells, and a mechanism of action whereby the prodrug upon administration enters the capsule and is converted into its active form by the cytochrome P450 expressed in the encapsulated cells" (Office Action, page 7). However, it is the Examiner's opinion that "[t]his is in fact an inherent characteristic of the encapsulated cells taught by Saller et al." (Office Action,

page 8). The Examiner further states that "the encapsulated cells taught by Saller et al. express cytochrome P450 protein, and the capsule allows prodrug molecules to pass into the capsule, wherein the prodrug molecules are converted into active drug molecules by cytochrome P450" (Office Action, page 8). The Examiner concludes that "claims 1-5, 7-20 are anticipated by Saller et al." (Office Action, page 8).

Applicants are not sure whether Claims 1-20 and 22 or Claims 1-5 and 7-20 are rejected as being anticipated by Saller *et al.* and respectfully request clarification. Applicants' claimed invention has been amended to more clearly recite a capsule comprising a porous membrane formed by a polyelectrolyte complex which encapsulates cells which express a cytochrome P450 gene, wherein the membrane is permeable to prodrug molecules, and the cytochrome P450 expressing gene and the cytochrome P450 expressed by the gene are retained within the capsule, and the use of the capsules to ablate tumor cells or to treat a tumor.

As pointed out in the Amendment mailed to the U.S. Patent Office on July 18, 2000, Saller *et al.* teach encapsulated cells which produce viral particles, wherein the viral particles produced by the encapsulated cells are released from the capsule (Saller *et al.*, page 7, Claim 1). Saller *et al.* also teach that the "viral particles produced by the encapsulated cells according to the invention, can be constructed to contain the genome of a viral vector carrying genes encoding marker and/or therapeutic genes", such as cytochrome P450 (Saller *et al.*, page 11). Thus, according to the teaching of Saller *et al.*, the viral particles pass from the capsules, the viral particles subsequently infect target host cells, and the genome of the viral vector, along with the gene encoding the marker/therapeutic gene present in the viral genome, is expressed within the infected host cell. Thus, according to the teachings of Saller *et al.*, the cytochrome P450 expressing cells are ***not*** retained within the capsule.

Saller *et al.* do not anticipate the subject matter of Applicants' claimed invention, particularly as amended.

Rejection of Claims 1, 5, 8, 9, 10, 11, 12 and 15-22 under 35 U.S.C. §103(a)

Claims 1, 5, 8, 9, 10, 11, 12 and 15-22 are rejected under 35 U.S.C. §103(a) "as being unpatentable over Wei et al. (Human Gene Therapy 5: 969-978, 1994) and Tai et al (FASEB Journal 7: 1061-1069, 1993)" (Office Action, page 8). The Examiner acknowledges that "one of ordinary skill in the art would not combine the teachings of Wei et al. and Tai et al. for the

purpose of encapsulating a cytochrome P450 expressing cell because cytochrome P450 would not 'pass out' of said capsule, one of ordinary skill in the art would have motivation to combine the teachings of Wei et al. and Tai et al. for the purpose of encapsulating a cytochrome P450 expressing cell because as taught by Wei et al. intrathecal administration of cytochrome P450 producing fibroblasts, followed by CPA, prevented meningeal neoplasia and led to partial regression of parenchymal solid tumors" (Office Action, page 9). The Examiner further states that "applicant points out that the cited art does not teach or suggest that a prodrug would enter the capsules comprising cells which express cytochrome P450 etc....", and notes that "the claims as currently amended do not limit the invention to such a mechanism of action" (Office Action, pages 9-10).

As amended, Applicants' claimed invention relates to a capsule comprising a porous membrane formed by a polyelectrolyte complex which encapsulates a cell which expresses a cytochrome P450 gene, wherein the membrane is permeable to prodrug molecules, and the cytochrome P450 gene and the cytochrome P450 expressed by the gene are retained within the capsule, and the use of the capsules to ablate tumor cells or to treat a tumor.

Wei *et al.* "demonstrate that C6 glioma cells, stably transfected with the P450 2B1 gene, become sensitive to CPA in culture" and that "intrathecal administration of P450 2B1-fibroblasts, followed by CPA, prevented meningeal neoplasia and led to partial regression of parenchymal solid tumors in the brains of athymic mice, previously seeded with rat C6 gliomas" (Wei *et al.*, page 969, column 2). Wei *et al.* do not teach or even suggest the use of a capsule for any purpose.

Tai *et al.* evaluated a new model of gene therapy by transforming "mouse fibroblasts with the human growth hormone gene (Ltk-GH) and showed that "Balb-c mice transplanted with the encapsulated Ltk-GH cells had detectable serum levels of human growth hormone (hGH) for the duration of the study (115 days)" (Tai *et al.*, page 1061, abstract). Tai *et al.* teach that it is essential that the gene product leave the capsule. Specifically, Tai *et al.* teach that:

> [t]he development of this model required that an appropriate semipermeable membrane be developed that would provide a microenvironment that is physiologically compatible with the growth of modified cells, *allow easy diffusion of the secreted gene products without compromising the immunoisolating properties of the membrane*, and maintain its biocompatibility properties after implantation (Tai *et al.*, page 1061, column 2).

In contrast, *the cytochrome P450 gene and the cytochrome P450 expressed by the gene are retained within Applicants' claimed capsules.*

In addition, as pointed out above, Tai *et al.* teach that the purpose of encapsulating cells is to immunoisolate the cells, *i.e.,* the capsule protects the encapsulated cells from being degraded by the immune system. Therefore, the pore size of the membrane must be small enough to prevent components of the immune system (*e.g.,* antibodies) from entering the capsule. According to the present invention, the cytochrome P450 is retained within the capsule and the prodrug must be able to enter the capsule through its porous membrane, where it is converted into its active metabolite by cytochrome P450. However, Tai *et al.* teach that the pore size of the capsule membrane must be small enough to prevent entry of components of the immune system. Therefore, based on the teachings of Tai *et al.*, a person of skill in the art would expect that such a pore size in the capsule would prevent entry of the prodrug into the capsule. That is, the person of skill in the art would expect that the capsule membrane would either be immunoisolating or permeable to the prodrug, but not both.

Even if, in contradiction to such an expectation, the prodrug would be able to enter an immunoisolating capsule, the skilled practitioner would expect that the active drug molecules would not be secreted from the capsule. As indicated above, for the purpose of the immunoisolation, Tai *et al.* direct the skilled practitioner to chose a small pore size for the capsule membrane. Consequently, a person of skill in the art would expect that the active drug molecules (cytotoxic drug) would not pass out of the porous membrane. Thus, the concentration of the cytotoxic drug would increase within the capsule and ultimately kill the encapsulated cytochrome P450 expressing cells. Therefore, a person of skill in the art would expect that long-term production of the cytotoxic drug would not be possible in such capsules.

However, Applicants show that implantation of the capsules in a tumor result in a dramatic reduction in size of the tumor (specification, page 29, lines 7-9) and that the encapsulated cells are nevertheless, protected against degradation by components of the immune system.

Considering Applicants' surprising and unexpected findings, it is clear that the combined teaching of Wei *et al.* and Tai *et al.* do not render obvious Applicants' claimed invention, particularly as amended.

Rejection of Claims 2, 4 and 5 under 35 U.S.C. §103(a)

Claims 2, 4 and 5 are rejected under 35 U.S.C. §103(a) "as being unpatentable over Wei et al. and Tai et al. as applied to claim 1, 8, 9, 15, 16, 17, 18 and 19 above in previous office action, and further in view of Merten et al. (Cytotechnology 7(2): Abstract, 1991)" (Office Action, page 11). The Examiner states that Merten *et al.* "teach a method for encapsulation of mammalian cells using capsules comprising cellulose sulphate and poly-dimethyl-diallyl-ammonium chloride (PDMDAAC)" (Office Action, page 11).

Applicants respectfully disagree. As pointed out above, the combined teaching of Wei *et al.* and Tai *et al.* Do not render obvious Applicants' claimed invention. Merten *et al.* do not provide what is lacking in the combined teachings of the Wei *et al.* and Tai *et al.* references. Merten *et al.* developed an encapsulation system in which capsules "were produced using a solution of sodium cellulose phosphate (CS) (1.5%) and poly-dimethyl-diallyl-ammoniumchloride (PDMDAAC)" and tested the "influences of varying encapsulation process parameters on capsule characteristics, cell growth, and monoclonal antibody production" (Merten *et al.*, page 121, abstract). Merten *et al.* do not teach or even suggest encapsulation of a cytochrome P450 expressing cell, the capsule comprising a porous membrane formed by a polyelectrolyte complex which encapsulates a cell which expresses a cytochrome P450 gene, wherein the membrane is permeable to prodrug molecules, and the cytochrome P450 gene and the cytochrome P450 expressed by the gene are retained within the capsule.

Clearly, the combined teachings of Wei *et al.* and Tai *et al.* in view of Merten *et al.* do not render obvious Applicants' claimed invention, particularly as amended.

Provisional Rejection of Claims 1-20 and 22 under the judicially created doctrine of obviousness-type double patenting

Claims 1-20 and 22 are rejected under the judicially created doctrine of obviousness-type double patenting "as being unpatentable over claims 13 and 15 of copending Application No. 08/996,460" (Office Action, page 12). The Examiner states that "[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other because they claim common subject matter, A capsule encapsulating a cytochrome P450 producing cell, said capsule comprising a porous membrane which allows prodrug to pass into the capsule, wherein the

cytochrome P450 producing cell line is a packaging cell comprising a retroviral vector carrying the cytochrome P450 gene" (Office Action, page 12).

Applicants' claimed invention has been amended to more clearly recite a capsule comprising a porous membrane formed by a polyelectrolyte complex which encapsulates cytochrome P450 expressing cells, wherein the membrane is permeable to prodrug molecules, and the cytochrome P450 gene and the cytochrome P450 expressed by the gene are retained within the capsule, and the use of the capsules to ablate tumor cells or to treat a tumor.

As pointed out in the Amendment mailed to the U.S. Patent Office on July 18, 2000, the invention described in U.S. Application No. 08/996,460, referred to herein as Saller *et al.*, does not render obvious Applicants' claimed invention. Saller *et al.* teach encapsulated cells which produce viral particles, wherein the viral particles produced by the encapsulated cells are released from the capsule (Saller *et al.*, page 7, Claim 1). Saller *et al.* also teach that the "viral particles produced by the encapsulated cells according to the invention, can be constructed to contain the genome of a viral vector carrying genes encoding marker and/or therapeutic genes", such as cytochrome P450 (Saller *et al.*, page 11). Thus, according to the teaching of Saller *et al.*, the viral particles pass from the capsules, the viral particles subsequently infect target host cells, and the genome of the viral vector, along with the gene encoding the marker/therapeutic gene present in the viral genome, is expressed within the infected host cell. Thus, according to the teachings of Saller *et al.*, the cytochrome P450 expressing cells are ***not*** retained within the capsule.

Saller *et al.* do not anticipate the subject matter of Applicants' claimed invention, particularly as amended.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Anne J. Collins

Anne J. Collins
Registration No. 40,564
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
Dated: October 15, 2001

MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

1. (Three times amended) A capsule [encapsulating a cytochrome P450 expressing cell, said capsule comprising a polyelectrolyte complex and a porous membrane which allows prodrug molecules to pass into the capsule, wherein the prodrug molecules are converted into active drug molecules by cytochrome P450] comprising a porous membrane formed by a polyelectrolyte complex which encapsulates cells which express a cytochrome P450 gene, wherein the membrane is permeable to prodrug molecules and the cytochrome P450 gene and the cytochrome P450 expressed by the gene are retained within the capsule.

9. (Twice amended) The capsule according to Claim 1 wherein the cytochrome P450 is cytochrome 2B1.

10. (Amended) A method for ablation of tumour cells, comprising contacting said tumor cells with prodrug molecules and a capsule [encapsulating a cytochrome P450 expressing cell, said capsule comprising a polyelectrolyte complex and a porous membrane which allows the prodrug molecules to pass into the capsule,] wherein the capsule comprises a porous membrane formed by a polyelectrolyte complex which encapsulates cells which express a cytochrome P450 gene, wherein the membrane is permeable to the prodrug molecules, the cytochrome P450 gene and the cytochrome P450 expressed by the gene are retained within the capsule and the prodrug molecules are converted into active drug molecules by cytochrome P450 and thereby ablate the tumor cells.

11. (Twice amended) A method of treating a tumor comprising administering to a subject in need thereof a therapeutically effective amount of a capsule [which encapsulates a cytochrome P450 expressing cell, said capsule comprising a polyelectrolyte complex and a porous membrane which allows a prodrug molecule to pass into the capsule, wherein the prodrug molecule is converted into an active drug molecule by cytochrome P450] and, either

simultaneously or with a time span, [the] a prodrug which is activated by cytochrome P450, wherein the capsule comprises a porous membrane formed by a polyelectrolyte complex which encapsulates cells which express a cytochrome P450 gene, the membrane is permeable to the prodrug molecules, the cytochrome P450 gene and the cytochrome P450 expressed by the gene are retained within the capsule and the capsule is introduced into the tumor or next to the tumor.

16. (Twice amended) The pharmaceutical kit according to Claim 15, wherein the capsules and the prodrug are formulated so that the capsules, which are administered into a target or next to the target, and the prodrug can be administered by different routes of administration.

22. (Amended) The capsule according to Claim 1 wherein the cytochrome P450 is [present in] encoded by a mammalian expression vector.